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LSD—An Historical Recollection

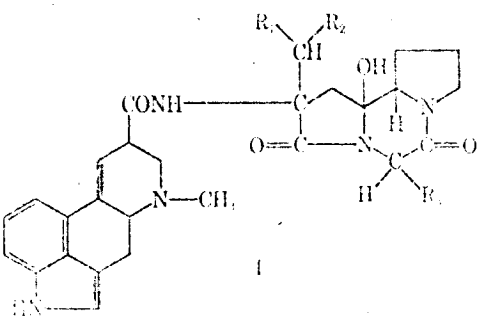
The most notorious psychedelic substance today is undoubtedly LSD. This drug has maintained its popularity in spite of other hallucinogens which have since been discovered. Simultaneously, it has enjoyed a vast amount of serious scientific investigation which has somehow become obscured in the wave of adverse publicity. It is the purpose of this paper to trace the chemical background of LSD, its synthesis, the discovery of its properties, and some of the research which has subsequently resulted (*1*).

Epidemics resulting from the ingestion of bread made from diseased grain were a common occurrence in the Middle Ages. The disease, now known as ergot poisoning, was then called Saint Anthony's fire—it was believed that a visit to the saint's shrine cured the malady. The illness was marked by vomiting, high temperature, tremors, and gangrene and convulsions in the later stages.

It was subsequently discovered that ergot poisoning was caused by a fungus, *Claviceps purpurea*, which thrived on the ears of various grains, most commonly rye. It was also found that the extract obtained from the mycelium portion of the fungus possessed medicinal properties. As early as 1582 these extracts were used to induce childbirth. However, the activity of the extracts varied tremendously from batch to batch. In spite of this drawback, use of the material continued and interest arose in the identity of the active principles of the extracts.

The first milestone was recorded in 1875 when a French chemist, Charles Tanret (*2*), succeeded in isolating the first crystalline substance from the extract. He named the material ergotinine. Unfortunately, ergotinine was not homogeneous. It was only in 1918 that Arthur Stoll, of the Swiss pharmaceutical company Sandoz, isolated ergotamine as the first pure ergot alkaloid (*3*). This marked the beginning of half a century of brilliant research in the area of ergot alkaloids led by Stoll and his close collaborator, Albert Hofmann.

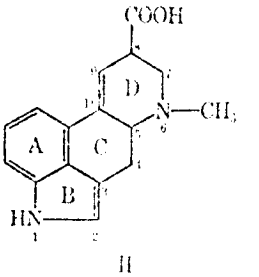
Mainly through the efforts of Stoll and Hofmann, it was established that nearly all ergot alkaloids of the lysergic acid type possess the general structure I.



I

They may be considered to be composed of two parts, the lysergic acid portion and the amide portion, the latter being a cyclic peptide made up of various amino acids.

This review will be limited to a discussion of the lysergic acid moiety. The classical chemical degradative studies carried out by Jacobs, Craig, and Gould (*4*) in this country and by Stoll and Hofmann (*5*, *6*) in Switzerland eventually led to the assignment of structure II to lysergic acid. Elucidation of this tetracyclic structure, also known as the ergoline ring system, took several years.



II

In 1945 Uhle and Jacobs (*7*) at Harvard synthesized racemic dihydrolysergic acid, and this synthesis provided unequivocal proof for the tetracyclic structure.

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However, the position of the olefinic double bond at either 9,10 or 5,10 remained to be settled, although studies by Stoll and Hofmann strongly suggested a 9,10 double bond.

This point was confirmed in 1954 when the total synthesis of racemic lysergic acid was finally achieved in a brilliant fifteen-step sequence. (*8*). The work, which was done in the Eli Lilly laboratories, is referred to as the Woodward synthesis. In the course of the synthesis over three hundred model compounds and intermediates were prepared. Previous attempts to synthesize lysergic acid had failed due to the inherent tendency of the molecule to undergo isomerization to the more stable naphthalenoid system. In the Woodward synthesis the difficulty was circumvented by an ingenious method which involved introduction of the 2,3-indole bond in the final step. The synthesis is schematically shown in Figure 1. To date this is the only published total synthesis of lysergic acid. Commercial lysergic acid (with the natural D configuration) is obtained by fermentation.

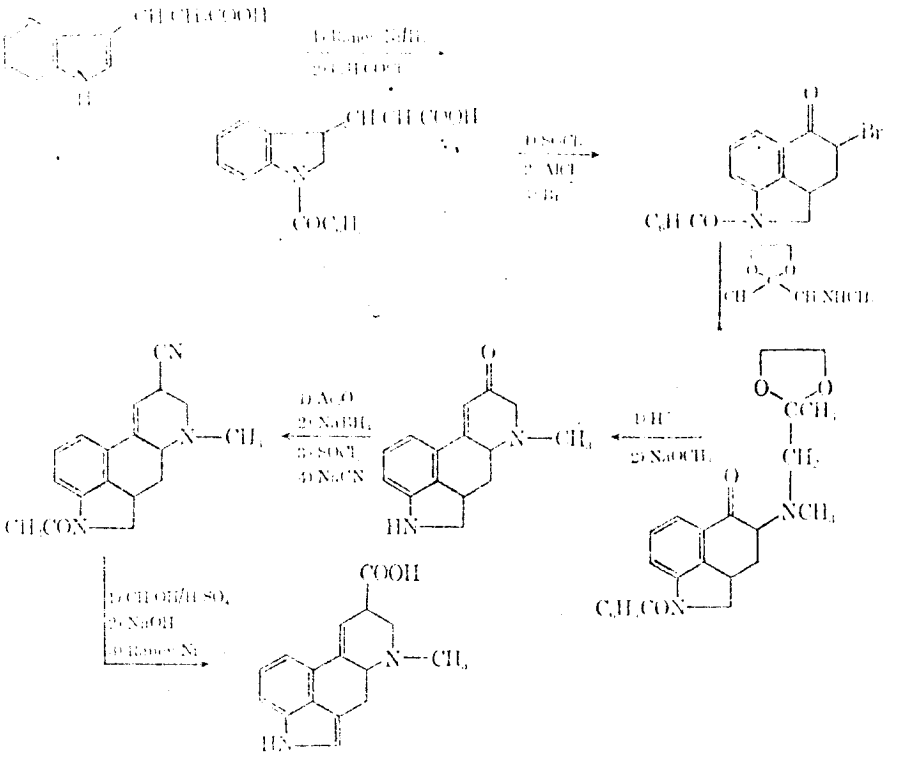
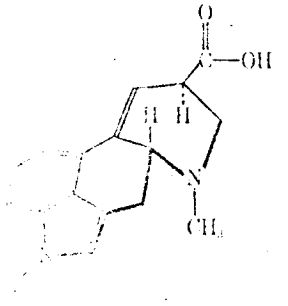


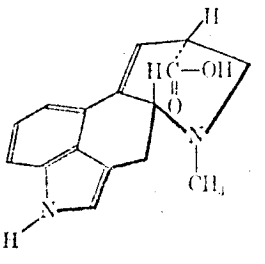
Figure 1. Total synthesis of lysergic acid.

The stereochemistry of lysergic acid is interesting from the chemical angle, and even from a general viewpoint, since correct stereochemistry is an important factor in maintaining physiological activity. As is evident from structure II, lysergic acid possesses two asymmetric centers at positions 5 and 8. Carbon 5 is the point of reference for distinguishing between the D and L isomers. By correlation with compounds of known absolute stereochemistry, it has been determined that all the natural ergot alkaloids belong to the D-series. The hydrogen atom at carbon 5 is above the plane of the molecule in the D-series, as shown in III (9).

The two isomers resulting from different configurations at position 8 were arbitrarily defined as normal and iso (*6*). In the normal isomer the carboxyl group is equatorial and on the same side of the plane of the molecule as the hydrogen atom at position 5, as seen in III. In contrast, the iso isomer (IV) possesses an axial carboxyl group which lies behind this plane. Isomerization occurs with great facility in the ergot alkaloids, especially in the free acid, and this was responsible for much of the confusion and difficulties in the early stages of the structural studies. The natural alkaloids occur in both iso and normal forms, although it is interesting to note that the iso isomers are practically devoid of physiological activity.



D-Lysergic Acid
III

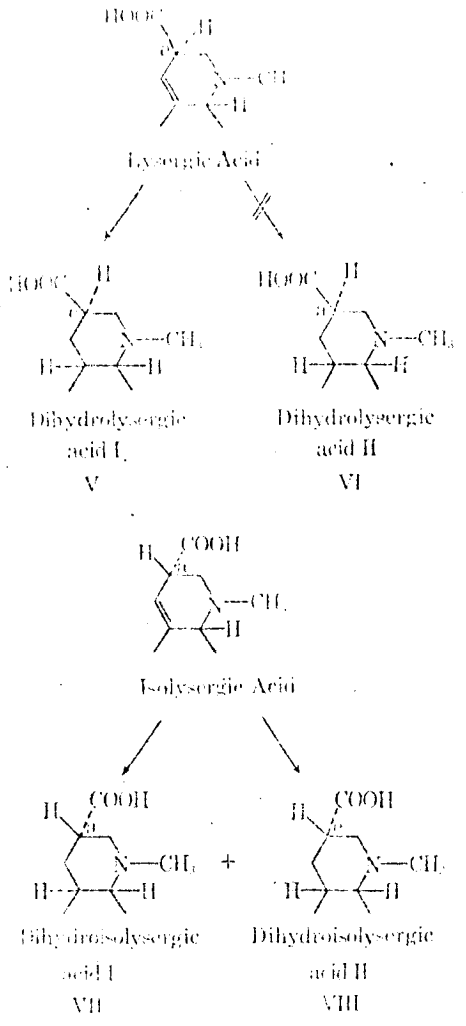


D-Isolysergic Acid
IV

Reduction of the 9,10-double bond gives rise to a new asymmetric center at position 10. Unless the reduction is stereospecific, the resulting product will be a mixture of two diastereoisomers with cis or trans fusion of rings C and D. Stoll and Hofmann (*10*) studied the catalytic hydrogenation of the normal and iso acids and the ergot alkaloids derived from them. They observed that, whereas the iso compounds yielded the two expected isomers VII and VIII, the normal alkaloids invariably gave only one product, V. Compound V was shown to have a CD-trans fusion. Preferential addition of hydrogen from the rear is explained by the steric hindrance caused by the carboxyl group at 8 and the hydrogen atom at 5 being on the same side of the molecule. The dihydrolysergic acid with a cis linkage of rings C and D (that is, VI) was obtained by isomerization of the corresponding iso compound VIII. The stereochemistry of the reduction products is shown at the top of the next page.

Concurrently with the research aimed at structural determinations, Stoll and Hofmann were also exploring the potential use of lysergic acid as a therapeutic agent. A natural consequence was the preparation of countless derivatives of the acid, namely, esters, amides, hydrazides, alcohols, and amines and their corresponding 9,10-dihydro derivatives.

In 1938 Stoll and Hofmann (*11*) reported the prepara-



tion of the diethylamide of lysergic acid. Nothing of particular interest was noted at the time, but in 1943, while reinvestigating the same compound, Hofmann had an experience which he later described in his own words (*12*)

> On a Friday afternoon, April 16, 1943, I was seized in the laboratory by a peculiar sensation of vertigo and restlessness. Objects in my vicinity and also the shape of my coworkers in the laboratory appeared to undergo optical changes. I was incapable of concentrating my mind on my work. In a dreamlike state, I left the laboratory and went home where I was seized by an irresistible urge to lie down and sleep. Daylight was felt to be unpleasantly intense. I drew the curtains and immediately fell into a peculiar state of "drunkenness," characterized by an exaggerated imagination. With closed eyes fantastic pictures of extraordinary plasticity and intensive kaleidoscopic colorfulness seemed to surge towards me. After two hours this state gradually subsided, and I ate dinner with good appetite, feeling perfectly normal and fresh.

A few days later Hofmann intentionally took by mouth 0.25 mg of the same drug, now known as LSD (after the German name, Lysergsäurediäthylamid), and experienced the same reaction. Perhaps this incident accounts for Hofmann's subsequent interest, including self-experimentation, in hallucinogenic or psychedelic drugs.

This does not imply that prior to Hofmann's discovery hallucinogenic substances were unknown. In fact, several were used in ancient religious rituals (*13*). For example, mescaline, the chief constituent of the Mexican cactus peyote, was used in sixteenth-century rites. Its structure was known about fifty years before that of LSD; its activity, however, is less by a factor of 5000–10,000. Psilocin and its phosphate derivative psilocybin, which occur in Mexican mushrooms, were isolated by Hofmann in 1958. They are 1/100–1/200 times as active as LSD. Bufotenin was isolated in the thirties, while harmine has been known for over a hundred years. Both substances were used in rituals by South American Indians. The structures of these hallucinogens are shown in Figure 2.

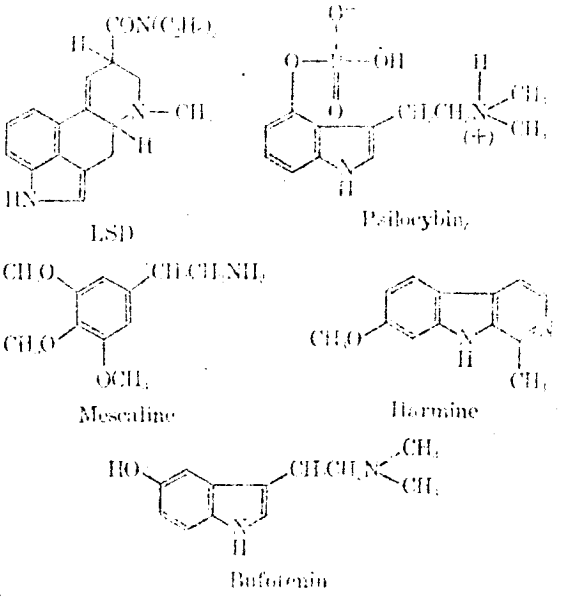


Figure 2. Some common hallucinogenic drugs.

None of these hallucinogens has gained the prominence enjoyed by LSD. This may be due to a combination of reasons, but perhaps the most outstanding is the extreme potency of LSD. The effective dose in man is 0.025–0.050 mg. This potency, however, varies in commercial preparations and is dependent on the ratio of stereoisomers present. LSD itself possesses the D and normal configuration as shown in the structure in Figure 2. Slight modifications of the basic structure usually result in a loss of hallucinogenic activity. This is summarized in Table 1 (*14*, *15*).

The effects of LSD do not seem to be influenced by the manner of drug intake (oral or intramuscular). In most cases reaction occurs within an hour, the height of the experience occurs in about four hours, and it is usually over in eight. However, the reaction is influenced by many other factors, such as age, personality, education, cultural background, motivation for taking LSD, and time of day when taken. These psychological aspects have been the subject of over a thousand papers which have appeared since Hofmann's original report on the hallucinogenic properties of LSD.

In spite of the great amount of research, the actual mechanism by which LSD functions in the body is still unknown. In the fifties it was a popular belief that the action of LSD was due to its serotonin antagonism. This was based on the then popular theory of Shaw and Wooley (*16*) that mental disorders were related to

Table 1. A Comparison of Psychic Effectiveness with Serotonin Antagonism

Compound	Psychic Effectiveness (Dose in man)	Serotonin-antagonistic Activity (LSD = 1)
D-Lysergic acid diethylamide (LSD)	0.5–1.0 μg/kg	1.0
L-Lysergic acid diethylamide	Inactive	<0.01
D-1-acetyl LSD	0.5–1.0 μg/kg	0.12
D-2-Bromo LSD	Inactive	2.0
D-9,10-Dihydro LSD	Inactive	0.62
D-2,3-Dihydro LSD	3.0–4.5 μg/kg	...
D-Lysergic acid methylamide	Inactive	0.065
D-Lysergic acid ethylamide	4.0–10.0 μg/kg	0.12
D-Lysergic acid propylamide	Inactive	0.40

body levels of serotonin, adrenaline, and acetylcholine. However, the theory as applied to LSD activity lost credence when 2-bromo LSD was synthesized and evaluated. As is evident from Table 1, the compound is a potent serotonin antagonist but has no hallucinogenic activity.

The pharmacological data on LSD are overwhelming. Over five hundred technical papers have been published. Table 2 presents a brief summary of the pharmacological effects. It should be pointed out that the type and degree of activity vary considerably from species to species.

What benefits has man derived from the knowledge so far gained in the study of LSD? This is a question that remains unanswered. LSD has been used to some extent in the treatment of schizophrenics. It is believed that the drug, when taken under skilled supervision, has provided greater rapport and ability to communicate for the patient undergoing therapy. There have also been claims that LSD is a potential analgesic (*17*) and has shown some value in the treatment of alcoholics (*18*). The claims are extremely tenuous but certainly provide some hope for the future of LSD.

Table 2. Summary of the Pharmacological Effects of LSD (1)

A. Central Actions Upon
  1. Psychic Functions
     - Excitation
     - Mood changes: euphoria, depression
     - Disturbances of perception
     - Hallucinations
     - Depersonalization
     - Schizophrenic state
  2. Somato-motor Functions
     - Pyramidal and extrapyramidal effects
     - Ataxia
     - Spastic paralysis
  3. Autonomic Nervous Functions
     a. Meso-diencephalic Effects
     - Mydriasis
     - Tachycardia
     - Rise in body temperature
     - Hyperglycemia
     - Pilomotor reaction

     b. Medullary or Bulbar Effects
     - Lowering of blood pressure
     - Bradycardia
     - Respiratory depression

B. Direct Peripheral Actions Upon
  - Uterus and vagina
  - Adrenergic functions
  - Vessels
  - Bronchi (in high doses)
  - Serotonin

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